REMARKS

Claims 31-41 and 46-61 were pending in this application. Claims 31, 33, 34, 38, 47, 50, 60 and 61 are currently amended without any intent of disclaiming equivalents thereof. Accordingly, upon entry of this paper, claims 31-41 and 46-61 are pending and presented for consideration.

Claim Amendments

Claims 31, 33, 34, 38, 47, 50, 60 and 61 are amended to correct informalities and for clarification and consistency. Applicants submit that the amendments to claims introduce no new matter.

Amendments to Specification

Applicants have amended the specification to capitalize the trademark SEPHAROSE® as requested by the Examiner. Applicants submit that the amendment to the specification introduces no new matter.

Rejections under 35 U.S.C. § 112, second paragraph

Claim 31 is rejected under 35 U.S.C. § 112, second paragraph, for allegedly failing to particularly point out and distinctly claim the subject matter. Specifically, the Examiner alleged that the term "the amount" recited in step (b) and the term "the ratio" recited in step (c) lack antecedent basis and it is not clear whether the term "vWF-antigen" in step (c) is referring to the "vWF-antigen" in step (b). Applicants have changed "the amount" in step (b) to "an amount," "the ratio" in step (c) to "a ratio," and "vWF-antigen" in step (c) to "the amount of vWF-antigen." Therefore, Applicants respectfully request the rejection of claim 31 be reconsidered and withdrawn.

Rejections Under 35 U.S.C. § 103(a) over Favaloro et al. in view of Christophe et al. and Hardin

Claims 31, 40, 41, 48-50 and 60 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Favaloro *et al.* (Pathology, 1993, 25:152-158) in view of Christophe *et al.* (Blood, 1994, 83:3553-3561) and Handin (U.S. Patent No. 5,321,127). Applicants traverse the rejection for the reasons enumerated below.

35 U.S.C. §103 states that the subject matter, taken as a whole, must be considered when evaluating the patentability of an invention under 35 U.S.C. §103. The consistent criteria for the determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that the claimed subject matter should be carried out and would have a reasonable likelihood of success. Both the suggestion and the expectation of success must be found in the prior art, not in Applicant's disclosure. *In re Dow Chemical Company*, 837 F.2d 469,473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention. *In re Fine*, 5 USPQ2d at 1600. Rather, there must be some teaching or suggestion supporting their use in the particular claimed combination. *See Smithkline Diagnostics, Inc. v. Helena Laboratories Corp.*, 859 F.2d 878, 887, 8 USPQ2d 1468, 1475 (Fed. Cir. 1988). For the reasons set forth below, Applicants respectfully submit that the skilled artisan would not have been motivated to combine the teachings of the primary reference with those of the secondary references cited by the Examiner to carry out Applicants' invention.

Claim 31 is directed to a method for detecting von-Willebrand disease using a soluble form or a portion of glycoprotein 1b(α) (GPlb(α)) and a ristocetin or a functionally equivalent substance. By contrast, the primary reference, Favaloro *et al.*, teaches a method for detecting von-Willebrand disease using collagen. Specifically, as set forth on page 153, in the paragraph under "Collagen binding assay for vWF," Favaloro *et al.* teaches a collagen-binding assay (CBA) for measuring vWF activity in a sample. Favaloro *et al.* does not teach or suggest using a soluble form or a portion of GPlb(α) and a ristocetin or a functionally equivalent substance to detect vWF activity as required by the method of claim 31. In fact, Favaloro *et al.* teaches away from using assays other than CBA including assays using ristocetin cofactor for detecting von-Willebrand disease. For example, as set forth on page 156, left column, Favaloro *et al.* states:

"Within the 'vWDII' patient group described above were four patient plasma samples which yielded assay results which may have otherwise been interpreted as normal in a more limited screening system (i.e. excluding the CBA assay, see Table 2)." In other words, Favaloro *et al.* indicates that its CBA assay has better performance characteristics than other assays. In particular, Favaloro *et al.* states that plasma samples that yielded normal (occasionally borderline) results in assays using ristocetin cofactor, all gave low CBA values in CBA assays. Therefore, Applicants submit that one of ordinary skill in the art upon reviewing Favaloro *et al.* would not have been motivated to replace its CBA assay with an assay using ristocetin cofactor for detecting von-Willebrand disease. Secondary references Christophe *et al.* and Handin teach assays using ristocetin cofactor, the very assays that Favaloro *et al.* suggests are inferior to Favaloro's CBA assay. Accordingly, Applicants submit that the skilled artisan, after reviewing Favaloro *et al.*, would not have been motivated to combine the teachings of Favaloro *et al.* with those of Christophe *et al.* and Handin especially when Favaloro suggests the CBA assay is superior. Applicants therefore respectfully submit that the Examiner's combination represents a hindsight reconstruction of the invention rather than a proper rejection, based on the perspective of one skilled in the art, as required by § 103.

Applicants further submit, even if the disclosures of Favaloro *et al.*, Christophe *et al.* and Handin were combined, such a combination would not teach Applicants' invention as claimed in claim 31. Claim 31 requires, *inter alia*, detecting von-Willebrand factor (vWF) activity in a sample using a soluble form or a portion of glycoprotein 1b(α) (GPlb(α)) and ristocetin or a functionally equivalent substance. As discussed above, Favaloro *et al.* teaches a method for detecting von-Willebrand disease using collagen. Specifically, Favaloro *et al.* teaches detecting vWF activity in a sample using collagen-binding assays. Favaloro *et al.* does not teach or suggest detecting vWF activity in a sample using a soluble form or a portion of GPlb(α) and ristocetin or a functionally equivalent substance as required by claim 31.

Christophe *et al.* does not correct the deficiency of Favaloro *et al.* Christophe *et al.* is directed to understanding the difference of the properties of plasma vWF from normal individuals and from patients with type IIA and type IIB von-Willebrand disease (*see, e.g.*, Christophe *et al.*, abstract and page 3554, left column and right column). Specifically,

Christophe *et al.* teaches a ristocetin induced platelet aggregation analysis to measure the binding affinities between vWF and insoluble GP1b receptors present on the surface of platelets. As set forth on page 3554, in the paragraph under "binding of plasma vWF and rvWF to platelet GP1b," Christophe *et al.* teaches using formaldehyde-fixed platelets in its platelet aggregation analysis. Christophe *et al.* does not teach or suggest use of a soluble form or a portion of GP1b(α) as required in claim 31.

Handin does not correct the deficiency of Favaloro *et al.* or Christophe *et al.* Although Handin teaches a specific fragment derived from Gp1b(α) (rGp1bαQ221-L318) that inhibits the ristocetin-dependent binding of vWF to platelets and the spontaneous binding of vWF to collagen (*see, e.g.*, Handin, column 3, lines 16-20), Handin is silent with respect to methods for disease detection of any sort, in particular, whether the rGp1bαQ221-L318 fragment taught by Handin would be useful to detect vWF activity in the presence of ristocetin or a functionally equivalent substance in order to detect von-Willebrand disease in a sample. Handin also does not provide an expectation of success that the rGp1bαQ221-L318 fragment can be used for detecting vWF activity.

Therefore, Applicants submit that the combination of Favaloro *et al.,* Christophe *et al.*, and Handin, even if proper, does not teach or suggest detecting vWF activity in a sample using a soluble form or a portion of GPlb(α) and ristocetin or a functionally equivalent substance as required in claim 31.

Accordingly, Applicants submit claim 31 and any claims dependent therefrom are novel and unobvious over Favaloro *et al.,* Christophe *et al.*, and Handin, either alone or in combination. Applicants therefore respectfully request reconsideration and withdrawal of the rejection of claims 31, 40, 41, 48-50 and 60.

Rejections Under 35 U.S.C. § 103(a) over Favaloro et al. in view of Christophe et al., Hoylaerts et al. and Handin

Claims 31-39, 41, 48-53 and 56-60 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Favaloro *et al.* in view of Christophe *et al.*, Hoylaerts *et al.* and Handin. Applicants traverse the rejection for the reasons enumerated below.

As discussed above, claim 31 and any claims dependent therefrom, including claims 32-39, 41, 48-53 and 56-60, are novel and unobvious over Favaloro *et al.*, Christophe *et al.*, and Handin, alone or in combination. Hoylaerts *et al.* does not correct the deficiency of Favaloro *et al.*, Christophe *et al.*, or Handin.

Hoylaerts *et al.* is directed to understanding how ristocetin mediates the binding of vWF to the GP1b complex (*see, e.g.*, Hoylaerts *et al.*, page 454, left column, first paragraph). Specifically, Hoylaerts *et al.* teaches an Elisa method for detecting the interaction between vWF and the GP1b protein complex in the presence of ristocetin. In the Office Action, the Examiner asserts that "Hoylaerts et al. teaches a method of detecting vWF activity in a sample (human plasma) using a soluble form or a portion of glycoprotein 1b(α) (GP1b(α)) and ristocetin (p454, Purification of Gp1b, Purification of vWF, and Studies of Interaction between vWF and GP1b)" (*see*, the Office Action, page 12). Applicants respectfully disagree with the Examiner's reading of Hoylaerts *et al.* On page 454, in the paragraph under "Studies of Interaction between vWF and GP1b," Hoylaerts *et al.* specifically teaches use of a GP1b protein complex containing both chains and the associated GPIX in its method. Therefore, contrary to the Examiner's assertion, Hoylaerts *et al.* does not teach or suggest use of a soluble form or a portion of GP1b(α) as required in claim 31.

Therefore, Applicants submit that claim 31 and any claims dependent therefrom are novel and unobvious over Favaloro *et al.*, Christophe *et al.*, Handin, and Hoylaerts *et al.*, either alone or in combination. Applicants therefore respectfully request reconsideration and withdrawal of the rejection of claims 31-39, 41, 48-53 and 56-60.

Rejections Under 35 U.S.C. § 103(a) over Favaloro et al. in view of any combinations of Christophe et al., Hoylaerts et al. and Handin and in further view of Batz *et al., Solen et al., or Vicente et al.*

Claim 54 stands rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Favaloro *et al.* in view of, Christophe *et al.*, Hoylaerts *et al.* and Handin, and in further view of Batz *et al.* (U.S. Patent No. 4,415,700). Claim 55 stands rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Favaloro *et al.* in view of, Christophe *et al.* and Handin, and in further view of Solen *et al.* (U.S. Patent No. 6,043,871) Claim 61 stands rejected under 35

U.S.C. § 103(a) as allegedly unpatentable over Favaloro *et al.* in view of, Christophe *et al.*, Hoylaerts *et al.* and Handin, and in further view of Vicente *et al.* (J. Biol. Chem., 1988, 263:18473-18479). Applicants traverse the rejections for the reasons enumerated below.

As discussed above, claim 31 and any claims dependent therefrom including claims 54, 55 and 61 are novel and unobvious over Favaloro *et al.*, Christophe *et al.*, Hoylaerts *et al.* and Handin, alone or in combination. None of the additional references, Batz *et al.*, Solen *et al.*, and Vicente *et al.*, corrects the deficiency of Favaloro *et al.*, Christophe *et al.*, Hoylaerts *et al.* or Handin discussed above. Applicants submit that Batz *et al.* teaches use of hydrophilic latex particles as carrier materials for biological and/or immunologically active substances in diagnostic agents (*see, e.g.*, Batz *et al.*, abstract and the first paragraph in detailed description). Solen *et al.* teaches a system and a method for measuring the platelet aggregation in whole blood in response to standard aggregating agents (*see, e.g.*, Solen *et al.*, abstract). Vicente *et al.* teaches a 45 KDa GP1b(α) N-terminal fragment that is capable of interacting with surface-bound vWF (*see, e.g.*, Vicente *et al.*, page 18475, left column). None of these additional references teach or suggest methods for detecting von-Willebrand disease of any sort. In particular, none of these additional references teach or suggest detecting vWF-activity in a sample using a soluble form or a portion of GPIb(α) and ristocetin or a functionally equivalent substance as required in claim 31.

Therefore, Applicants submit claim 31 and any claims dependent therefrom including claims 54, 55 and 61 are novel and unobvious over Favaloro *et al.,* Christophe *et al.*, Hoylaerts *et al.*, Hardin, Batz *et al.*, Solen *et al.*, and Vicente *et al.*, either alone or in any combinations. Applicants therefore respectfully request reconsideration and withdrawal of the rejections of claims 54, 55 and 61.

CONCLUSION

Applicants believe that all of the art of record has been overcome and claims 31-41 and 46-61 are in condition for allowance. The Examiner is invited to telephone the undersigned agent to discuss any remaining issues. Early and favorable actions are respectfully solicited.

Respectfully submitted,

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